Citation:

Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest.* 2009 May;119(5):1322-34. Epub 2009 Apr 20.

PubMed ID: 19381015

Study Design:

Nonrandomized Clinical Trial

Class:

C - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess the relative effects of glucose and fructose during sustained consumption in humans, by answering the following questions:

- Does consumption of fructose with an ad libitum diet promote greater body weight gain and have differential effects on regional adipose deposition and adipose gene expression compared with consumption of glucose with an ad libitum diet?
- Does consumption of fructose induce dyslipidemia compared with consumption of glucose?
- Is fructose-induced hypertriglyceridemia the results of increased rates of hepatic DNL and/or decreased triglyceride clearance?
- Does consumption of fructose decrease glucose tolerance and insulin sensitivity?
- Are there differences between the responses of older men and postmenopausal women to dietary fructose?

Inclusion Criteria:

- Overweight and obese subjects aged 40 -72 years
- BMI 25 - 35 kg/m^2
- Self-report of stable body weight during the prior 6 months
- Women were considered postmenopausal based on a self-report of no menstruation for at least 1 year

Exclusion Criteria:

- Evidence of diabetes

- Renal or hepatic disease
- Fasting serum triglyceride concentrations greater than 400 mg/dL
- Hypertension (>140/90 mm Hg)
- History of surgery for weight loss
- Individuals who smoked
- Those reporting exercise of more than 3.5 hours per week at a level more vigorous than walking
- Reported having used thyroid, lipid-lowering, glucose-lowering, antihypertensive, antidepressant, or weight-loss medications
- Habitual ingestion of more than 1 sugar-sweetened beverage per day or more than 2 alcoholic beverages per day

Description of Study Protocol:

Recruitment

Participants were recruited through newspaper advertisements and underwent a telephone and in-person interview with medical history, complete blood count, and serum biochemistry to determine eligibility.

Design: This was a double-blinded parallel arm study that used matched subjects and consisted of 3 phases (a) a 2-wk inpatient baseline period during which subjects consumed an energy-balanced diet; (b) an 8-wk outpatient intervention period during which subjects consumed either fructose- or glucose-sweetened beverages providing 25% of daily energy requirements along with their usual ad libitum diet; and (c) a 2-wk inpatient intervention period during which subjects consumed fructose- or glucose-sweetened beverages providing 25% of daily energy requirements with an energy-balanced diet. Sugars were provided to the subjects as 3 daily servings of glucose- or fructose-sweetened beverages flavored with an unsweetened drink mix (Kool-Aid; Kraft). During the outpatient intervention, subjects were instructed to drink 3 svgs/d, 1 with each meal, and not to consume other sugar-containing beverages including fruit juice during the study protocol.

Blinding used (if applicable): double-blind

Intervention (if applicable)

- During the 2-week baseline phase of the study, subjects resided in the UCD Clinical and Translational Science Center's Clinical Research Center and consumed an energy-balanced, high-complex carbohydrate (55%) diet
- Subjects consumed glucose- or fructose-sweetened beverages providing 25% of energy requirements for 8 weeks with self-selected ad libitum diets.
- Subjects consumed glucose- or fructose-sweetened beverages providing 25% of energy requirements for 2 weeks with energy-balanced diets

Statistical Analysis

- Mean values were determined
- Response variables were analyzed using ANOVA with Tukey's multiple comparison post tests
- Effects of individual sugars were analyzed by 2-tailed paired Student's t tests

Data Collection Summary:

Timing of Measurements

Measurements made at baseline, and after 2, 8 and 10 weeks.

Dependent Variables

- Body weight
- 24-hour serial blood collection
- 26-hour stable isotope infusion for determination of fractional DNL
- Fasting and postprandial postheparin blood sampling
- Oral glucose tolerance test and disposal test
- Gluteal adipose biopsy
- CT scan of the abdomen

Independent Variables

- During the 2-week baseline phase of the study, subjects resided in the UCD Clinical and Translational Science Center's Clinical Research Center and consumed an energy-balanced, high-complex carbohydrate (55%) diet
- Subjects consumed glucose- or fructose-sweetened beverages providing 25% of energy requirements for 8 weeks with self-selected ad libitum diets.
- Subjects consumed glucose- or fructose-sweetened beverages providing 25% of energy requirements for 2 weeks with energy-balanced diets
- Dietary intake measured through 24-hour food-intake recall interviews conducted on 6 outpatient days

Control Variables

Description of Actual Data Sample:

Initial N: 39 subjects enrolled in the study.

Attrition (final N): 32 subjects, 17 in the fructose group (9 males, 8 females), 15 in the glucose group (7 males, 8 females). 7 subjects (3 in the glucose group, 4 in the fructose group) did not complete the study because of inability/unwillingness to comply with protocol or due to personal or work-related conflicts.

Age:

- Mean age of males in glucose group = 54 ± 3 years
- Mean age of females in glucose group = 56 ± 2 years
- Mean age of males in fructose group = 52 ± 4 years
- Mean age of females in fructose group = 53 ± 2 years

Ethnicity: not reported

Other relevant demographics:

Anthropometrics

There were no significant differences between groups at baseline anthropometric characteristics or any of the measured metabolic parameters.

Location: California

Summary of Results:

Key Findings

- Body weight was stable during the 2-wk inpatient periods at both the beginning and end of the study. However, during the 8-wk outpatient intervention period, when the subjects consumed 25% of daily energy requirement as glucose- or fructose-sweetened beverages along with ad libitum self-selected diets, both groups exhibited similar significant increases in body weight. Percent changes in body weight after consumption of glucose- or fructose-sweetened beverages for 10 wks were +1.8 ± 0.5 ($P < 0.01$) and +1.4 ± 0.3 ($P < 0.001$), respectively.
- Although both groups exhibited similar weight gain during the intervention, visceral adipose tissue was significantly increased only in the subjects consuming fructose
- Fasting plasma triglyceride concentrations increased by approximately 10% during 10 weeks of glucose consumption but not after fructose consumption
- In contrast, hepatic de novo lipogenesis and the 23-hour postprandial triglyceride AUC were increased specifically during fructose consumption.
- Similarly, markers of altered lipid metabolism and lipoprotein remodeling, including fasting apoB, LDL, small dense LDL, oxidized LDL, and postprandial concentrations of remnant-like particle-triglyceride and -cholesterol significantly increased during fructose but not glucose consumption
- In addition, fasting plasma glucose and insulin levels increased and insulin sensitivity decreased in subjects consuming fructose but not in those consuming glucose

Baseline Values and Percentage Changes in Body Composition After Consumption of Glucose- or Fructose-Sweetened Beverages for 10 Weeks

Outcome Variables	Glucose (0 weeks)	Glucose (% change)	Fructose (0 weeks)	Fructose (% change)
Body weight (kg)	85.9 ± 2.7	+1.8 ± 0.5, $P < 0.01$	85.7 ± 2.6	+1.4 ± 0.3, $P < 0.001$
Total body fat (kg)	30.7 ± 2.2	+3.2 ± 0.6, $P < 0.001$	28.9 ± 2.2	+2.8 ± 1.0, $P < 0.01$
Waist circumference (cm)	94.6 ± 2.6	+1.7 ± 0.6, $P < 0.05$	94.7 ± 2.7	+1.9 ± 0.4, $P < 0.001$
Total abdominal fat (cc)	765 ± 57	+4.8 ± 2.1	683 ± 55	+8.6 ± 3.0, $P < 0.05$
Extraabdominal fat (cc)	522 ± 59	+4.6 ± 1.4, $P < 0.05$	476 ± 43	+7.3 ± 4.0
Intraabdominal fat (cc)	243 ± 21	+3.2 ± 4.4	207 ± 21	+14.0 ± 5.5, $P < 0.01$

Author Conclusion:

These data suggest that dietary fructose specifically increases de novo lipogenesis, promotes dyslipidemia, decreases insulin sensitivity, and increases visceral adiposity in overweight/obese adults.

Reviewer Comments:

Small numbers of subjects in groups. Dietary differences between the 3 intervention periods.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	???
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	???
2.4.	Were the subjects/patients a representative sample of the relevant population?	???

3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A

5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes

	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		???
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	No
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes